REMARKS

Claims 1, 2 and 4-20 are pending in the instant application. Claims 1, 2 and 4-20 have been rejected. Claims 3, 11 and 16-20 have been canceled. Claims 1 and 15 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. **Rejection of Claims Under 35 U.S.C. 112, Second Paragraph**

Claims 1, 2, 4-10 and 12-20 have been rejected under 35 U.S.C. 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner suggests that it is unclear if the reference to SEQ ID NO: 3 refers to the SHH protein or the nucleic acid molecule encoding SHH. Applicants have amended claim 1, and by dependency claims 2, 4-10 and 12-20, to refer to a nucleic acid molecule of SEQ ID NO: 3. Withdrawal of this rejection is respectfully requested.

II. **Rejection of Claims Under 35 U.S.C. 112, First Paragraph**

Claims 15-20 have been rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification is enabling for antisense-mediated inhibition of SHH expression *in vitro*, but the Examiner suggests that it does not reasonably provide enablement for antisense-mediated inhibition of SHH expression *in vivo* or their use in methods to treat disease. The Examiner cites several articles on the technology of antisense to support his position Applicants respectfully traverse this rejection.

Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* is highly unpredictable.

The Examiner has pointed to articles concerning the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

What these papers cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans. Nowhere in the references cited do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

The paper by Braasch and Corey (2002) describes the advances that have been made in the design of antisense compounds over the years. Included in the discussion are the types of advances that are taught in the specification as filed. Nowhere in the reference do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*. In fact, the paper states in the abstract that success in clinical trials with these agents has occurred.

The paper by Tamm et al. (2001) is another more recent review of the antisense technology and its specific application to oncology. Again, although the use of antisense is discussed in terms of what can go wrong, the paper again describes advances such as those taught in the instant specification. Nowhere in the reference do the authors state or suggest that results of well-

designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

The paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The papers by Gewirtz et al. (1996) and Agrawal (1996) are older papers not relevant to the state of the art of antisense compounds in 2001, the filing date of the instant application. Both papers discuss in general terms issues that were related to older antisense technology. However, nowhere do these papers state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

However, Applicants have amended claim 15 to recite that the method is performed *in vitro* in an earnest effort to advance the prosecution and facilitate the allowance of this case. Claims 16-20 have been canceled with Applicants reserving the right to file a continuing application directed to this subject matter without prejudice. Withdrawal of the rejection is requested in light of these amendments.

III. Rejection of Claims Under 35 U.S.C. 102

Claims 1, 2, 4, 5, 11, 12, 14 and 15 have been rejected under 35 U.S.C. 102(b) as being anticipated by Sadler et al. (1997). The Examiner suggests that this reference teaches a 20 mer antisense oligonucleotide that is inhibits SHH and is phosphorothioated, hybridizes to an active site on SHH and is administered in a pharmaceutically acceptable carrier. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended the claims to refer to antisense compounds that are targeted to a specific nucleobase region within the coding region of SHH (SEQ ID NO: 3). Support for this amendment can be found throughout the specification as filed but in particular at pages 83-85, Table 1. In this table, the region of the coding region is defined by targeting nucleobase regions with antisense compounds. One such antisense compound is shown to target a region that begins with nucleobase 501 while others are shown to be active by targeting adjacent nucleobases, up to nucleobase 926.

Sadler et al. (1997) disclose use of an antisense oligonucleotide targeted to the 3' end, 998 bases downstream from the ATG initiation codon, which should be a region that begins at

nucleobase 1135 according to SEQ ID NO: 3. No other antisense compounds targeted to SHH are taught or suggested by this reference, including compounds targeted to nucleobases 501 through 926 as now claimed. In order to anticipate a claim the cited reference must teach each and every limitation of the claim (MPEP 2131). This reference fails to teach the limitations of the claims as amended and thus cannot anticipate the instant invention. Withdrawal of this rejection is respectfully requested.

Claims 1, 2, 4, 5, 11, 12, 14 and 15 have been rejected under 35 U.S.C. 102(e) as being anticipated by Ingham et al. (US Patent 6,165,747). The Examiner suggests that this patent discloses the use of antisense oligonucleotides, 20 mer, to inhibit expression of SHH of SEQ ID NO: 3, wherein the antisense compounds are phosphorothioated and wherein they hybridize to an active site on SHH and are administered in a pharmaceutically acceptable carrier. Applicants respectfully traverse this rejection.

Ingham et al. (US Patent 6,165,747) disclose the use of antisense compounds in general to inhibit expression of SHH. No specific target regions within SEQ ID NO: 3 are taught or suggested by this reference, nor are any specific antisense compounds shown to have activity to inhibit expression of this gene. Nowhere does

this patent teach or suggest antisense compounds as now claimed that are targeted to a specific region within the sequence of SHH. In order to anticipate a claim the cited reference must teach each and every limitation of the claim (MPEP 2131). This reference fails to teach the limitations of the claims as amended and thus cannot anticipate the instant invention. Withdrawal of this rejection is respectfully requested.

IV. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 4-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Ingham et al. or Sadler et al., in view of Taylor et al. (1999) and Baracchini et al. (US Patent No. 5,801,154). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill to incorporate the oligonucleotide modifications of Baracchini et al. into the modified antisense compounds targeting SHH of SEQ ID NO: 3 as taught by Sadler et al. or Ingham et al. The Examiner suggests on would have been motivated to create such compounds because Sadler and Ingham teach that the modified oligonucleotides are resistant to degradation and Baracchini et al. teach that further modification increase uptake and antisense activity. The Examiner suggests one of skill would have had an expectation of success

based on the teachings of Taylor et al. and Baracchini et al. Applicants respectfully traverse this rejection.

As discussed *supra*, claim 1 and its dependent claims have been amended to recite antisense compounds targeted to a specific region of SHH of SEQ ID NO: 3. Support for this amendment to the claims can be found throughout the specification as filed but in particular at pages 83-85.

Also as discussed *supra*, neither of the primary references cited by the Examiner (Sadler et al. and Ingham et al.) teach or suggest antisense compounds as now claimed which are targeted to a specific region within the sequence of SHH of SEQ ID NO: 3. It is only with the specification in hand that one of skill would understand which regions could be successfully targeted with antisense compounds as claimed. Therefore, these primary references, either alone or when combined with other references, fail to teach the limitations of the amended claims.

The secondary references cited fail to overcome the deficiencies in teaching of the primary references.

Taylor et al. (1999) is a review article on antisense technology. Nowhere does this paper teach or suggest that a particular region as now claimed, within the sequence of SHH, could

be successfully targeted with antisense compounds directed to SHH.

Baracchini et al. (US Patent 5,801,154) teach methods of modifying antisense oligonucleotides to enhance activity. However, nowhere do this patent teach or suggest antisense oligonucleotides targeted to SHH, or any region of a SHH nucleic acid molecule.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims as amended, which claim antisense compounds targeted to a specific region of a nucleic acid molecule encoding SHH, and thus cannot render the instant claimed invention obvious. Moreover, a mere teaching of the concept of antisense for a gene does not give one the expectation of success for using antisense as disclosed in the instant invention. It is only with the specification in hand that one of skill would understand that the claimed region could be successfully targeted

with antisense compounds and result in inhibition of SHH gene expression. Withdrawal of this rejection is therefore respectfully requested.

V. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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